GENZYME EUROPE BV
GOOIMEER 10
1411 DD NAARDEN
NETHERLANDS
Tel: +31-35-699-1200
Fax: +31-35-694-3214

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Direct Healthcare Professional Communication on the supply of *Fabrazyme®* *(agalsidase beta)*
Further extension of the delay in the normal supply and recommendations on treatment for patients experiencing clinical deterioration

Dear Healthcare Professional,

Following the recent communication in February 2010 announcing that the supply of Fabrazyme would return to normal levels by the end of June 2010, Genzyme wishes to **inform you about a further extension of the Fabrazyme shortage and provide updated treatment recommendations.**

- Genzyme detected an equipment defect at the Allston manufacturing site leading to a continuation of the Fabrazyme supply shortage on the European market. **Until at least the end of September 2010, Genzyme will only have sufficient Fabrazyme to meet 30% of the global demand.**

- Genzyme is hereby providing temporary treatment recommendations in order to ensure that patients with Fabry disease continue to receive adequate treatment. **The treatment recommendations as communicated in the DHPC of September 2009 are to remain in place.**

- **Based on spontaneous adverse events reports, an increase in clinical manifestations indicative of Fabry disease progression has been observed on lowered dose. Pain, cardiac manifestations and deafness are usual manifestations of Fabry disease. Patients on lowered dose should remain under close surveillance and for those experiencing aggravation of disease symptoms and/or adverse events ascribed to the lowered dose of Fabrazyme, physicians are advised to reinitiate the treatment with the original dosing regimen or initiate a treatment with alternative approved medicinal product.**

- All patients, especially those with adjusted dose regimens should be under close clinical surveillance. A medical examination, including all relevant clinical parameters, should be performed every two months. It is of the utmost importance to monitor the plasma GL-3 or urinary GL-3 levels, as for the moment the GL-3 level is the most sensitive parameter.

- Adverse events should be reported in the usual manner and health care professionals are reminded to document batch numbers in the patient record.

These are temporary recommendations and do not change the currently approved Product Information for Fabrazyme. The recommendations only apply until the supply problems have been resolved.

Should you require any further information, please contact the Genzyme entity in your country via e-mail xxx or telephone xxx.

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Yours sincerely,

Carlo Incerti, MD.
Head of R&D Europe

Annex: Fabrazyme treatment recommendation, September 2009

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European Medicines Agency
Press office

London, 25 September 2009
Doc. Ref. EMEA/602583/2009

PRESS RELEASE
Supply shortage of Fabrazyme – updated treatment recommendations required for adult male patients

The European Medicines Agency has been informed by Genzyme, the marketing authorisation holder of Fabrazyme (agalsidase beta), that the supply shortage of the medicine is more severe than previously expected. The Agency's Committee for Medicinal Products for Human Use (CHMP) has therefore agreed to new temporary treatment recommendations, saying that not only female but also male patients should receive a reduced dose of Fabrazyme. These recommendations revise the recommendations proposed by the company in June 2009.

The updated recommendations during the supply shortage are as follows:

- Children and adolescents (<18 years) should receive Fabrazyme according to the recommended dose and frequency.
- Adult male patients and adult female patients already treated/stabilised may receive Fabrazyme with an adjusted dose of 0.3 mg/kg as maintenance dose every two weeks.
- Patients with adjusted dose regimens should be under close clinical surveillance. A full medical examination, including all relevant clinical parameters, should be performed every two months. It is of the utmost importance to monitor the plasma GL-3 or urinary GL-3 levels, as for the moment the GL-3 level is the most sensitive parameter. Patients who demonstrate a deterioration of disease should reinitiate the original treatment with Fabrazyme.

These are temporary recommendations and do not change the currently approved Product Information for Fabrayme. It is expected that these changes will need to continue until the end of the year.

Fabrazyme is used in the treatment of patients with Fabry disease, a rare, inherited enzyme-deficiency disorder in which patients do not have enough of an enzyme called alpha-galactosidase A. The deficiency in this enzyme causes certain fat molecules to accumulate in the body's tissues, particularly the heart, kidneys, eyes and nerve tissue.

The supply shortage is caused by the shutting down of Genzyme's production site for Cerezyme and Fabrazyme in Allston Landing, in the United States of America in June 2009, because viral contamination (calicivirus of the type Vesivirus 2117) required sanitisation of the bioreactors. Therefore, the CHMP issued temporary changes to the way Cerezyme and Fabrazyme are prescribed and used in June 2009 to ensure that patients could continue to have access to these medicines while Genzyme was solving the manufacturing issues.

In August 2009, the Agency had to update the temporary changes for Cerezyme following notification by the company that the existing stocks for this medicine were lower than previously communicated.

Genzyme has now informed the Agency that inventories of Fabrazyme will also be lower than anticipated because of low yields of the enzyme after the manufacturing process was restarted.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 09
E-mail: mail@emea.europa.eu http://www.emea.europa.eu